REMARKS/ARGUMENTS

Claims 26-28, 41-43, and 51-53 are presently pending, and will remain pending upon entry of the instant response to the record. *No new matter has been added.*

Moreover, amendment and/or cancellation of the claims during pendency of the application are not to be construed as acquiescence to any of the objections/rejections set forth in any Office Action, and were done solely to expedite prosecution of the application. Applicants submit that claims were not added or amended during prosecution of the instant application for reasons related to patentability. Applicants reserve the right to pursue the claims as originally filed, subsequently amended or added, or similar claims, in this or one or more subsequent applications.

Preliminary Matters:

As a preliminary matter, the Examiner has suggested that the IDS filed August 14, 2009 "is not a proper submission in accordance with MPEP §609 and 37 C.F.R. 1.98." Applicants have investigated the source of this confusion, and have found that the IDS document submitted by electronic filing on August 14, 2009 (which was, in fact, "EFS Web 2.1.16" Form PTO/SB/08a (07-09)) was somehow altered by the filing system after the document was uploaded to PAIR. As such, we trust that this error may be simply rectified by re-submission of the document. In order to prevent additional error, Applicants provide a identical copy that has been scanned in to prevent re-formatting of the information. Accordingly, Applicants respectfully request that the Examiner consider these references.

Claim Rejections under 35 USC §103

Rejection of Claims 26-28, 41-43, and 51-53 under 35 USC §103(a)

The Examiner has maintained the rejection of claims 26-28, and 41-43, as well as rejected newly added claims 51-53, under 35 USC §103(a) as being unpatentable over Bradbury et al. in view of Hsu et al. and Nelson et al. Applicants respectfully traverse this rejection

In this regard, the prosecution of related applications in foreign jurisdiction is understandably not mandatory precedent for Examiner's at the USPTO. However, before providing a response, Applicants suggest that the issued patents of major jurisdictions, such as Europe and Japan, should provide a reasonably persuasive position to the US Examiner, and

highlight the defendability of the pending claims upon any necessary appeal. In this regard, and as a mere convenience, Applicants have appended the related issued patents from Europe and Japan (with associated machine translated claims) to this response. For emphasis, Applicants provide the relevant claims below, excerpted from the related European patent:

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Claims

1. The use of *N*-(3-methoxy-5-methylpyrazin-2-yl)-2-(4-[1,3,4-oxadiazol-2-yl]phenyl)pyridine-3-sulphonamide, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of cancer in a warm blooded animal such as man.

2. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the reduction of abnormal proliferation in a cancerous cell or inducing differentiation of a cancerous cell in a warm blooded animal such as man.

3. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in inducing apoptosis in a cancerous cell in a warm blooded animal such as man.

4. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as an anti-angiogenic and vascular targeting agent in blood vessels supplying a cancerous cell in a warm blooded animal such as man.

5. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as an anti-angiogenic agent in a warm blooded animal such as man.

6. The use according to claim 1 wherein the cancer is oesophageal cancer, myeloma, hepatocellular, pancreatic, cervical cancer, ewings tumour, neuroblastoma, Kaposis sarcoma, ovarian cancer, breast cancer, colorectal cancer, prostate cancer, bladder cancer, melanoma, lung cancer - non small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), gastric cancer, head and neck cancer, renal cancer lymphoma and leukaemia.

7. The use according to claim 1 wherein the cancer is prostate cancer.

8. The use according to claim 1 wherein the cancer is SCLC, NSCLC, colorectal cancer, ovarian cancer and / or breast cancer.

9. The use according to claim 1 wherein the cancer is bladder cancer, oesophageal cancer, gastric cancer, melanoma, cervical cancer and / or renal cancer.

10. The use according to claim 1 wherein the cancer is endometrial, liver, stomach, thyroid, rectal and / or brain cancer.

11. The use according to claim 1 wherein the cancer is SCLC.

12. The use according to claim 1 wherein the cancer is NSCLC.

13. The use according to claim 1 wherein the cancer is colorectal cancer.

14. The use according to claim 1 wherein the cancer is ovarian cancer.

15. The use according to claim 1 wherein the cancer is breast cancer.

16. The use according to any one of claims 1 and 6-15 wherein the cancer is in a metastatic state.

17. The use according to any one of claims 1 and 6-15 wherein the cancer is in a non-metastatic state.

18. The use according to any one of claims 1 and 6-15 wherein the cancer is renal, thyroid, lung, breast or prostate cancer that is producing bone metastases.

19. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use as an inhibitor of bone metastases and an inhibitor of invasion in a warm blooded animal such as man.

20. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of medicament for use as an inhibitor of bone metastases in a warm blooded animal such as man.

21. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the prevention of bone metastases in a warm blooded animal such as man.

22. The use of the compound according to claim 1, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the treatment of bone metastases in a warm blooded animal such as man.

Alternatively, the Japanese issued claims are limited to prostate cancer due to the stringent data requirements of Japanese patent law. Applicants emphasize that the claims of the instant application have been amended to facilitate prosecution by adopting the prostate cancer limitation of the Japanese issued claims. Accordingly, Applicants request consideration of the patent claims that issued in the related applications prosecuted in these *major* international jurisdictions in support of the arguments already presented in the record and those described herein.

ARGUMENTS DIRECTED TO PRIMA FACIE CASE FOR OBVIOUSNESS

With respect to the arguments directed to the prima facie case for obviousness, the Examiner has indicated that she is not persuaded by the arguments of Applicants prior response, and again reiterates the suggestion of the prima facie case for obviousness laid out in the prior office action. However, in doing so, the Examiner lays out some flawed reasoning and a number of inaccurate characterizations, to which Applicant provides the following response.

In general, the flawed reasoning relates to the prima facie case for obviousness, and the very nebulous use of references to arrive at the present invention. ***The Examiner fails to make a proper prima facie case for obviousness by failing to understand the art of the ordinarily skilled artisan attempting to solve the problem solved by the present invention.*** In this respect, the *central* flaw in the Examiner's argument stems from the selection of the Bradbury et al reference as a starting point (from which the Hsu et al and Nelson et al references are argued to complete the solution to the problem). This initial selection, as Applicants previously attempted to introduce, would not present itself in a search during an investigation by the ordinarily skilled artisan of the problem to be solved in the instant application (without the benefit of hindsight).

Applicants believe this analysis merits emphasis:

In ascertaining the prior art that would be before the ordinarily skilled artisan, the ordinarily skilled artisan would be presented *first* with the problem to be solved.

In the instant application, the problem to be solved (as further defined by the pending claims) is the treatment of prostate cancer. However, Bradbury et al. is not in the "sea" of cancer art, and only tangentially indicates "certain cancers."

Moreover, a person standing in the shoes of the ordinarily skilled artisan who is looking to identify the solution to the problem of treating prostate cancer would certainly not begin this search with Bradbury et al, which is primarily related to the description of a number of ET-1 antagonists useful for the treatment of a variety diseases, particularly cardiovascular disorders, *e.g.*, congestive heart failure. As such, the Examiner's initial reference is clearly selected using impermissible hindsight reconstruction, standing in the shoes of the instant Applicants, who through inventive contribution had selected Compound (I) as a starting point.

Even if one were to begin with a reference that would solve the problem that the instant invention solves, the ordinarily skilled artisan would not have been specifically directed to the ET-1 antagonists of Bradbury et al., which at the time of filing the instant application were one among numerous references directed to ET-1 antagonists. Applicants respectfully remind the Examiner that the analysis is not whether one of ordinary skill in the art **could** combine the references, its whether one of ordinary skill in the art **would** have combined these particular references in such a selective manner faced with numerous other references related to ET-1 antagonists, for example, by some motivating factor. Applicants assert that the ordinarily skilled artisan would have been so motivated.

Even further removed from this motivation would be to select ***one*** particular compound among the 70 other listed compounds; a compound that was clearly noted in the instant specification on page 3, lines 14-18, to have unexpected properties in the treatment of cancer due to its individual exceptional activity related to its lack of measurable activity at ET_B

> There is no hint or suggestion from …[the prior art]…that this compound would possess the particular beneficial efficacious, metabolic and toxicological profiles that makes it such a potent anti-cancer agent. In fact, the present inventors have surprisingly established that Compound **(I)** is a specific endothelin-A (ET_A) antagonist and has no measurable activity against endothelin-B (ET_B).

And although the Examiner has suggested that the alternative embodiments by their mere recitation in Bradbury et al. provide support for selection of the particular example (i.e., Compound (I)), this is not true if this reference were the *secondary* reference to which the ordinarily skilled artisan would be motivated to consult/combine with the disclosure of the primary reference solely to provide a portion of the missing solution to the problem presented, which in this case would be the very compound itself.

Applicants respectfully assert, particularly in light of the European and Japanese patents issued above (under the well-known scrutiny of these jurisdictions), that the Examiner has not and could not meet the appropriate burden to establish a *prima facie* case for obviousness.

ARGUMENTS DIRECTED TO SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS

Even assuming for arguments sake that the Examiner had established a prima facie case for obviousness, Applicants strenuously remind the Examiner that ***secondary considerations of nonobviousness may be used to rebut this determination***. The Examiner has seemingly erroneously interpreted the introduction of these advantages as arguments related to the finding of a prima facie case for obviousness, see page 7 of the instant Office Action:

> The fact that some endothelin-A antagonists have measurable and undesirable endothelin-B properties drifts away from the issue. What is at issue in the present case is whether the prior art provides a *prima facie* case of obviousness as to why one of skill in the art would have employed the compound of Bradbury et al….

The Examiner further implicates a lack of distinction between prima facie obviousness and secondary considerations of nonobviousness, by suggesting that "…the question of whether the compound is an ET_A or ET_B antagonist is clearly a peripheral issue because the prior art provides an unambiguous reason to employ the instantly claimed compound for treating prostate cancer outside of its function as an antagonist of either the endothelin-A or endothelin-B."

Applicants respectfully refute this logic, and assert that this reasoning is not in accordance with the principles of MPEP §2145. In no circumstance, is the Examiner allowed to unilaterally suggest that secondary considerations should not be considered in the obviousness determination; particularly for which a nexus has been established between the rebuttal evidence and the claimed invention. For example, MPEP §2145 recites

> If a *prima facie* case of obviousness is established, the burden shifts to the applicant to come forward with arguments and/or evidence to rebut the *prima facie* case. See, e.g., In re *Dillon,* 919 F.2d 688, 692, 16 USPQ2d 1897, 1901 (Fed. Cir. 1990)…
>
> Office personnel should consider all rebuttal arguments and evidence presented by applicants. See, e.g., *Soni*, 54 F.3d at 750, 34 USPQ2d at 1687....
>
> Rebuttal evidence may include evidence of "secondary considerations," such as "commercial success, long felt but unsolved needs, [and] failure of others." *Graham v. John Deere Co.*, 383 U.S. at 17, 148 USPQ at 467. See also, e.g., *In re Piasecki*, 745 F.2d 1468, 1473, 223 USPQ 785, 788 (Fed. Cir. 1984)…

Accordingly, Applicants respectfully request a reconsideration of the unexpected properties described in the specification, and highlighted in Applicants prior response, related to endothelin-A specificity (no measurable ET_B activity) in a more appropriate fashion under guidance of MPEP §2145. For clarity, this property could not have been predicted by the art, and as such, it could not have been predicted Compound (I) would be such a suitable agent for the treatment of prostate cancer.

Moreover, Applicants also provided an article with our prior response, which emphasized the "failure of others" for the very reason that Compound (I) of the instant invention is successful and unexpected, *i.e.*, highlighting the importance of ***ET_A specificity coinciding with the lack of measurable ET_B activity***.

This article discusses ZD4054 (Compound **(I)**) and the Phase II clinical trial results, and asserts that the compound has been "shown to improve the **overall survival** of men with hormone-resistant metastatic prostate cancer." (emphasis added) This article also contrasts ZD4054 (Compound **(I)**) with Atrasentan, another endothelin antagonist in clinical trials that has not shown the overall survival benefit, which was suggested to be:

> …due to the fact that it also inhibits signaling mediated by the endothelin-B receptor, which is thought to promote apoptosis and slow tumor spread. ZD4054 seems to have the advantage of not inhibiting endothelin-B receptor activity.

It is not exactly clear how the Examiner has simply dismissed these secondary considerations, which, in fact, provide strong support for the nonobviousness of the instant claims. However, perhaps this confusion may be due to the Examiner's misunderstanding and mischaracterization of the roles of ET_A and ET_B, as captured on pages 6-7 of the present Office Action:

> …Bradbury et al. already acknowledges that the compounds disclosed therein are both functional antagonists of ET-1 receptors *and* that they

> are also therapeutically effective for the treatment of certain cancers. The very teaching that such compounds are useful for the treatment of cancers clearly indicates that Bradbury et al. would not [have] employed such compounds for the purpose of interfering with the apoptotic process because, as Applicant has even admitted on the record, interfering with or stopping the process of apoptosis would have prevented normal cell death and promoted tumor growth…

This reasoning is completely faulty (and a mischaracterization of Applicants recitation in the specification on pages 3-4); if no more evident than in the Atrasentan clinical trials (described in the submitted reference and summarized above), which has been established for use in prostate cancer clinical trials, yet has shown significant failures suggested as related to the inhibition of "signaling mediated by the endothelin-B receptor, which is thought to promote apoptosis and slow tumor spread." The inhibition of endothelin-B receptor had never been considered by the ordinarily skilled artisan as a deterrent to election as a prostate cancer therapeutic, until the instant application. However, by the Examiner's logic, Atrasentan could not possibly have endothelin-B receptor activity for the very reason that it was selected as a prostate cancer therapeutic. A conclusion that clearly flies in the face of what is known, and therefore proves the Examiner's logic is faulty.

In contrast, it should be understood in light of the disclosure of the instant application that endothelin-B receptor activity does not preclude use as an anti-cancer agent, but rather the lack of endothelin-B receptor activity significantly improves a compounds use as an anti-cancer agent by not blocking synergistic pro-apoptotic pathways. It is this property of Compound (I) that motivated the Applicants to select it for use in treating prostate cancer; a motivation that would not have been evident from the prior art.

In addition, for the sake of clarifying the record, the roles of ET_A and ET_B are not "alleged," as suggested by the Examiner on page 6 of the Office Action, but are rather supported by *unrebutted* documentary *evidence* in the form of a reference; as well as initially described in the specification of the instant application to which the Applicants are entitled to the presumption of operability (unless contradicted by evidence supplied by the Examiner).

As such, and particularly in light of these findings, the fact that Compound **(I)** is such a suitable agent for use in treating prostate cancer could not have been predicted from any of the prior art teachings, particularly when known selective endothelin A antagonists have measurable and undesirable, endothelin B properties.

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Accordingly, Applicants respectfully request withdrawal of the rejection of claims 26-28, 41-43, and 51-53 under 35 USC §103(a), and favorable reconsideration.

Claim Rejections under Obviousness-Type Double Patenting

Rejection of Claims 26-28, 41-43 and 51-53 under Obviousness-Type Double Patenting

Claims 26-28, 31-32 and 41-43 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 42-44 of co-pending U.S. Application No. 11/720,001 in view of Bradbury et al. (U.S. Patent No. 5,866,568; 1999), Hsu et al., and Nelson et al. Applicants request that this *provisional* rejection be held in abeyance, and suggest that such rejection will be addressed once the present application is considered allowable but for this *provisional* obviousness-type double patenting rejection.

Rejection of Claims 26-28, 41-43, and 51-53 under Obviousness-Type Double Patenting

Claims 26-28, 41-43, and 51-53 stand provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 42-44 of co-pending U.S. Application No. 12/483,821 in view of Bradbury et al, Hsu et al., and Nelson et al. Applicants request that this *provisional* rejection be held in abeyance, and suggest that such rejection will be addressed once the present application is considered allowable but for this *provisional* obviousness-type double patenting rejection.

Request for Phone Interview

Once the Examiner has had an opportunity to review the comments made herein, Applicants respectfully request a phone interview with the *Examiner and the Examiner's SPE* in order to discuss any final details that may help result in an allowance of the application with all pending claims.

CONCLUSION

Applicants respectfully request favorable reconsideration of all rejections/objections. As noted above, if a telephone conversation with Applicants' attorney would help to expedite the prosecution of the above-identified application, the Examiner is urged to call Applicants' attorney at the telephone number below.

The above amendments have been made without prejudice to Applicants right to prosecute any cancelled subject matter in a timely filed continuation application.

Although Applicants believe no fees are due, the Commissioner is hereby authorized to charge any deficiency in the fees or credit any overpayment to deposit account No. 50-3231, referencing Attorney Docket No. 100815-1P US.

Respectfully submitted,

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